May 19, 1950.

Dear Gordon:

From your letter, I can see that we are both floundering in different parts of the same mire. One of the interesting conclusions that can be drawn is that the haploid prototrophs arise from the same sort of peturbed mechanisms as can be seen in the diploid heterozygotes. Some of these peturbations (vide my letters of March 20 and 24) may help to understand (in " ") what you are running into.

Since S^r is apparently closely linked to Mal, and shows the same shenanigans, I think that it is possible that your difficulties in finding S^r Az^r complementaries may be due to their non-existence in most meoises, much as you find both "complementaries" in your nutritional selections to be Mal-. If so, then this is not so suitable a technique after all, unfortunately. If find it a little difficult to follow your letter in detail, because I don't see just how your factors were coupled in the crosses, but I should be able to infer this.

There is really no independent evidence that S is linked to M; the inference is based on the frequency of S^r in prototrophs, and the assumption that this is regulated principally by linkage to M+. The assumption is false, so the conclusion may be also. Superimposed on the (probable) true linkages, there is this mysterious directed segregation (possibly by linkage to equally mysterious haplo-lethal deletions), and in addition the homozygosis [by intercalary meiosis and refusion?] for factors which should be heterozygous. I am a little surprised that even the hints of linear linkage that do persist can be seen through this mess. But there is enough confusion already amply to cover such paradoxes as the "100% crossing-over" between P and T. You may indeed be selecting for T+, perhaps not extrinsically, but simply as a feature of the non-random segregation of alternative alleles that I still hope can be explained in terms of deletions introduced into the diplophase.

Recently Iahave been trying to find evidence that some feature of coli genetics may be stochastic, and I may have it in <u>mutation</u>. I mentioned in 3/24 H-226 which is Lac_1^- Lac_4^+ Mal- //Lac_1^+ Lac_4^- Mal+ , i.e., phenotypically Lac v Mal v and that Mal-(homozygous) Lac V "partial segregants" rarely occur from H-226. One of these was Lac v Xyl v Mal- (H-238). I have been obtaining revesse mutations for Mal from H-238, and testing the revert diploids, now heterozygous for Mal and Xyl, for the linkage phase [coupling or cis, and repulsion or trans] of these two markers, which are quite closely linked in the diploid. A fair number of such tests have been made, and essentially equal numbers of the independently occurring reversions have been in the two phases, showing that the two allels, which are derived from the same mutation, have an equal mutability. The success of this experiment provides unequivocal support for the test for hemizygosity (failure of reversions to segregate) which is the basis of the idea of deletions or deficiencies in the diploid. (Mal y is very exceptional; almost all diploids have been Mal- hemizygous.)

Just one other research item: a mutation in K-12 which makes for a constitutive lactase. Later I found that this was the same as one of the Lac+ suppressors of Lac_3- (Glu- Mal- Lac-).

I am very sorry that you are not going to have time to finish this work at leisure, but I hope thatbthis may provide you with some incentive to take it up again after your internship. Zinder has made some very good progress with sexuality in Salmonella typhimurium during the last two weeks and you might perhaps amuse yourself by thinking about the potentialities. I don't have to mention again how stimulating I would find your collaboration, and my consequent unwillingness to regard the subject as closed.

Will I see you in Columbus this September?

Sincerely,

Joshua Lederberg